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WILLIAM J MCNICHOL JR
REED SMITH SHAW & MCCLAY
2500 ONE LIBERTY PLACE
1650 MARKET STREET
PHILADELPHIA, PA 19103-7301

EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/202,549	TSICHLIS ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☒ Claim(s) *21 and 22* is/are allowed.

6)☒ Claim(s) *1-8,10,11,23 and 24* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed August 27, 2003. Amendments were made to the claims.

Claims 1-24 are pending in the instant application. Claims 12-20 are withdrawn from consideration. Claims 1-11 and 21-24 are under consideration in the instant Office Action. Any rejection of record in the previous Office Action, mailed August 26, 2003, that is not addressed in this action has been withdrawn.

Applicant's objection to the nature of the previous Office Action as running "afoul of the established patent examining procedure" is noted. The current Office Action bears the signature of a Primary Examiner, thereby satisfying the guidelines set forth in MPEP § 706.04. Furthermore, it is believed that the previous Office Action contained legitimate rejections despite a previous indication of allowability, and that the iteration of the nature of the rejections in combination with the responses to Applicant's arguments clearly sets forth why claims that were previously allowed were subsequently rejected. Applicant is reminded that the Office does not perpetuate errors for the sake of procedure.

Claim Objections

Claims 7 and 8 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claims 7 and 8 recite that the claimed Gfi-

1 binding site prior to mutation can be as little as 65% or 79% homologous to a Gfi-1 binding site. Thus, claims 7 and 8 read on a genus of sequences that are much broader in scope than the genus of sequences set forth in the parent claim. As such, claims 7 and 8 fail to further limit claim 1.

Maintained Rejections

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The primary focus of the rejection is that the instant specification does not provide a written description of a representative number of the genus of sequences being 65% and/or 79% homologous to SEQ ID NO: 2 that are capable of binding to the Gfi-1 transcriptional repressor prior to their mutation. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Response to Arguments Regarding Claim Rejections - 35 USC § 112, First Paragraph

Applicant's arguments filed August 27, 2003 have been fully considered but they are not persuasive. Applicant's arguments consist of the following points:

1. That the instant specification, from page 19, line 17 through page 20, line 15, and from page 24, line 12 through page 26, line 6 describe a number of binding sequences with 65% and 79% homology to the Gfi-1 consensus binding site that are capable of binding to Gfi-1 prior to mutation.

2. That random oligonucleotide selection, described at page 14 line 29 through page 15, line 15 shows an actual reduction of practice of sequences having 65% and 79% sequence homology to the Gfi-1 consensus binding site that are capable of binding Gfi-1 prior to mutation.

3. That a number of *potential* (emphasis added) Gfi-1 binding sites are listed in Table 2, and that each of these sequences has the AATC-motif, showing a structural feature that is common to all Gfi-1 binding sites.

Applicant's arguments have been considered but are not convincing for the following reasons:

1. Contrary to Applicant's assertion, there is no indication from page 19, line 17 through page 20, line 15 of any Gfi-1 binding sequence, let alone a Gfi-1 binding sequence that has as little as 65% or 79% homology to the Gfi-1 consensus binding sequence. The same is true of the instant specification from page 24, line 12 through page 26, line 6. It would appear that the argument is predicated on a showing that is incorrectly represented (i.e., applicant has indicated the wrong location in the specification; otherwise, it would appear the statements are unsupported).

However, because the basis of Applicant's assertion is unclear from the indicated pages, it is impossible to address the argument within the context suggested by the Applicant.

2. The random oligonucleotide selection, described at page 14 line 29 through page 15, line 15 does not actually reduce to practice any Gfi-1 binding sequence, let a lone a sequence with as little as 65% or 79% binding activity. Rather, it simply sets forth a procedure that can be used to identify potential Gfi-1 binding sites. This does not provide a written description of the Gfi-1 binding site because a method to identify a sequence does not provide the necessary structure-function relationship required to satisfy the written description requirement of a claim.

3. It is noted that Table 2 references a number of *potential* Gfi-1 binding sites (it is also noted that none of these sequences has less than 79% homology to the consensus sequence). However, it is unclear which of these sequences is an *actual* Gfi-1 binding sequence. Therefore, one of skill in the art could not determine a structure-function relationship for a Gfi-1 binding site based on these sequences. The AATC-motif sequence appears to be necessary for Gfi-1 binding, although there are a number of sequences that lack the AATC-motif that are capable of binding to Gfi-1. However, this does not mean that all AATC-motif containing sequences are capable of binding Gfi-1. For example, a sequence having 65% homology to the consensus binding sequence can have as many as 4 different residues changed within the context of the binding site. Presuming that the AATC-motif must be maintained, the skilled artisan would make mutations outside of that region. An example of a sequence that fits such a description within the confines of SEQ ID NO: 2 is *A*AAATCA*AAA*A, where the residues that are changed are italicized and the required site is underlined. Curiously, this sequence is absent from Table 2. The question that is raised is, "Is this sequence, which is 65% homologous to the consensus Gfi-

1 binding site, capable of binding to Gfi-1?" The specification does not make this clear, either implicitly or explicitly; therefore the written description has not been satisfied. Thus, Applicant's statement that the AATC-motif is sufficient to establish a structure-function relationship for a Gfi-1 binding site is in doubt. In order for the AATC-motif to be an identifying structural feature for a given function, it must necessarily result in the function when present in a structure. However, there is no clear indication in the specification that all AATC-motif containing sequences are Gfi-1 binding sequences.

The written description issue is amplified by the fact that it is unclear whether or not the AATC-motif must actually be maintained in order to meet the limitations of the claims. This is supported by the fact that there were some oligomers that bound to Gfi-1, but did not contain an AATC-motif (see for example the instant specification, page 19, lines 21-23-7% of the Gfi-1 binding sequences had no AATC-motif). Presuming the inclusion of a sequence that does not contain the AATC-motif within the sequences that have 65% or 79% homology to the consensus binding site (since up to 4 residues can be altered within the sequence-including the AATC-motif of the consensus sequence), the claims now read on a sequence that does not have an AATC-motif, yet binds to Gfi-1 prior to its mutation. The skilled artisan has no hope of envisioning such a sequence, let alone what mutations can be made to such a sequence in order to abrogate Gfi-1 binding. Thus, the skilled artisan could not envision the broad genus of sequences indicated in the claims, therefore the claims do not satisfy the written description requirement.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10-11 and 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The focus of the rejection is that the nature of a Gfi-1 binding site is indefinite as set forth in the claim and the instant specification. The position of the Office is that the metes and bounds of the Gfi-1 binding site is indefinite because it is unclear if the sequence relates to the consensus Gfi-1 binding site, which encompasses the AATC-motif characterized as critical for the binding of the Gfi-1 transcriptional repressor, or if it also encompasses other Gfi-1 binding sites such as those that do not contain the AATC-motif. **This rejection is maintained for the reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 112, Second Paragraph

Applicant's arguments filed August 27, 2003 have been fully considered but they are not persuasive. Applicant's arguments consist of the following points:

1. That one of skill in the art would understand the metes and bounds of the Gfi-1 binding site irrespective of an indication of the Gfi-1 binding site as the consensus sequence, or any particular sequence. This is because (i) the instant specification, from page 11, line 9 through page 12, line 37, teaches that "Gfi-1 is a nuclear protein...functions as a transcriptional repressor...promoter contains two sites with 79% and 80% homology to the Gfi-1 binding *consensus* (emphasis added)," and (ii) this teaching is not clear as to whether the claim is referring to the consensus binding site or another binding site, but is still not idefinite.

Applicant's arguments have been considered but are not convincing for the following reasons:

1. (i) The metes and bounds of a claim cannot be determined by points within the limitations of a claim; rather, they must be determined by the endpoints of a claim. In the instant argument, Applicant has provided two examples of Gfi-1 binding sites (from the HCMV promoter, having 79% and 80% homology with the consensus site) that fall within the metes and bounds of the claim. However, these examples do not define the metes and bounds of the claim, because it does not aid in the determination of what other sequences fall within the scope of the claim (i.e., does a sequence with 45% homology to the consensus sequence, or a sequence without the AATC-motif, fall within the metes and bounds of the claim?). Therefore, this argument alone is insufficient to persuade the examiner of the definiteness of the claim. (ii) Although Applicant asserts in their argument that the teaching of the HCMV Gfi-1 binding sites have no relation to the consensus site, the examiner disagrees. In fact, the statement indicates that these sequences have homology *to the consensus site*. The indefiniteness of the claim resides primarily with the fact that there are sequences with little apparent homology to the consensus site, yet retain the ability to bind Gfi-1. It is unclear if these sequences (i.e., the 7% of Gfi-1 binding sequences that lack and AATC-motif) are included within the scope of the claims, and if so, what the nature of the sequences and their critical Gfi-1 binding sites is. For purposes of clarifying the nature of the rejection, this rejection is now expanded upon under 35 USC § 112, first paragraph, enablement.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-11 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection not necessitated by amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is an enhancer element that has been mutated so as to disrupt the binding of the Gfi-1 transcriptional repressor. The purpose of the mutation is to enhance transcription of a gene of interest from a promoter containing an enhancer element that, prior to mutation, bound the Gfi-1 transcriptional repressor. In order to make and use the invention, the skilled artisan would be required to know which sequences actually bound to the Gfi-1 transcriptional repressor; i.e., what the Gfi-1 binding sequence encompassed. In

some embodiments, the sequence is *any* sequence that binds to Gfi-1 (e.g., claim 1). In some embodiments of the invention, the Gfi-1 binding site prior to mutation is as little as 65% (claim 7) and 79% (claim 8) homologous to a Gfi-1 consensus binding site (SEQ ID NO: 2). In some embodiments, the sequence is the Gfi-1 binding site consensus sequence (e.g., claim 9).

Scope of the invention. The scope of the invention is very broad, encompassing *any* sequence that can bind to Gfi-1. The specification establishes a consensus binding site, identified as SEQ ID NO: 2, based on the binding of Gfi-1 protein to selected oligonucleotides. Of these oligonucleotides, 92% contained an AATC-motif that was shown to be vital for the binding of the Gfi-1 transcriptional repressor; this was because mutation of the AATC-motif abolished Gfi-1 binding. Of these oligonucleotides, 7% of the Gfi-1 binding sequences did not contain the AATC-motif, and these sequences are not further described in the specification. The scope of the invention includes not only the mutated sequences that contained the AATC-motif as represented in the consensus binding sequence prior to mutation, but also the mutated Gfi-1 binding sequences that contained no AATC-motif prior to mutation.

State of the art and Level of skill in the art. The state of the art at the time of filing is silent with regard to the Gfi-1 binding site, as well as mutations within the site that would abrogate Gfi-1 binding. Thus, the skilled artisan would be required to consult the instant specification in order to make and use the claimed invention.

Number of working examples and Guidance provided by applicant. The instant specification provides significant guidance with respect to one class of Gfi-1 binding sequences (those containing the AATC-motif in the consensus binding sequence), but very little guidance with respect to a second class of Gfi-1 binding sequences (those not containing the AATC-

motif). The instant specification clearly indicates that, in the consensus Gfi-1 binding site, mutations of the AATC-motif are capable of prohibiting the binding of Gfi-1. Thus, when using a promoter element containing the consensus Gfi-1 binding site, the skilled artisan would clearly understand that mutations in the AATC-motif would be sufficient to reduce the binding of Gfi-1 to the enhancer, thereby enhancing transcription from that promoter element. However, the specification teaches that a portion of Gfi-1 binding sites (within the broad scope of the claims) do not contain such an AATC-motif, as does the consensus binding sequence (see for example page 19, lines 21-23 of the instant specification). The skilled artisan would not be able to make mutations in a promoter element having a Gfi-1 binding site that did not contain the consensus binding site with the AATC-motif, such that the promoter no longer bound to Gfi-1. This is because the skilled artisan cannot identify the sequences of the Gfi-1 binding sequences that do not have the AATC-motif, nor can the skilled artisan reasonably make a mutation that would prevent the binding of Gfi-1 in such a sequence. This is because these sequences are not provided in the instant specification, nor are they characterized to indicate the nucleotides that are important for binding Gfi-1. Thus, the skilled artisan would not be able to make or use the claimed invention commensurate with the scope of the claims because the skilled artisan cannot identify non-AATC-motif containing Gfi-1 binding sites, let alone mutate those sites in such a manner to abrogate the binding of Gfi-1.

Unpredictability of the art and Amount of experimentation required. The full scope of the invention is highly unpredictable as it regards making and using Gfi-1 binding sequences that have been mutated in such a manner to prevent the binding of the Gfi-1 transcriptional repressor. While the skilled artisan would clearly understand that mutating the residues in the AATC-motif

of the consensus Gfi-1 binding site would result in a promoter element with enhanced transcriptional activity, the skilled artisan would not be apprised of what mutations to make in a Gfi-1 binding site that did not contain an AATC-motif so that Gfi-1 would no longer bind to this sequence. In order to make such a sequence, the skilled artisan would have to perform undue and unpredictable trial and error experimentation. First, the skilled artisan would have to identify what non-AATC-motif containing sequences were capable of binding to Gfi-1 without an ability to predict which sequences were capable of binding to Gfi-1. Then the skilled artisan would have to identify the critical residues involved in the binding of Gfi-1 in order to uncover which mutations in these Gfi-1 binding sites were capable of abrogating Gfi-1 binding, and therefore uncovering the mutations that could be used to enhance transcription from a promoter encompassing such a Gfi-1 binding site. This represents an invitation to empirical experimentation, where the skilled artisan is required to uncover the identity of the additional Gfi-1 binding sites, as well as the critical Gfi-1 binding site nucleotides. As such, the claim is not enabled for the full scope of Gfi-1 binding sites.

In conclusion, the skilled artisan would understand where to make a mutation in the consensus Gfi-1 binding site, where the AATC-motif was present prior to mutation. The skilled artisan would also know to make the mutation in the AATC-motif itself, as the instant specification teaches that this is where the critical nucleotides for Gfi-1 binding are located. However, the skilled artisan would not know where to make mutations in the 7% of Gfi-1 binding sites that do not contain an AATC-motif. This is because none of these sequences are described or characterized with respect to the nucleotides that are critical for Gfi-1 binding. Without a disclosure of these sequences (which are within the broad scope of the claims), and

their critical residues, the skilled artisan could not make the appropriate mutation in the sequence without unpredictable and undue trial and error experimentation.

Allowable Subject Matter

Claims 21-22 are allowed.

Claim 9 is objected to as being dependent on a rejected claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER